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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

ASHEN, JON BENJAMIN

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/966,724

Applicant(s)

KINZLER ET AL.

Examiner

Jon B. Ashen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26,27 and 56 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26,27 and 56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application/Amendment/Claims

1. Claims 27, 28 and 56 are pending in this application. Claims 1-26, 29-55 and 57-61 were cancelled by Applicant.

Applicant's response filed 5/31/05 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 02/28/05 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

2. The benefit of priority of claims 27, 28 and 56 is considered to be the filing date of Application 07/867,840, which is 04/07/1992.

Claim Rejections - 35 USC § 112

3. Claims 27, 28 and 56 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the Action mailed 02/28/2005.

Response to Arguments

Applicant's arguments filed 5/31/2005 have been fully considered but they are not persuasive. Applicant has argued that, one skilled in the art, at the time the application was filed, would have understood that the inventors had possession of the recited "antisense oligonucleotides which are complementary to human MDM2 mRNA for use in the claimed *in vitro* methods of treating cells. One skilled in the art would have understood that Applicants had possession of a human MDM2 mRNA based on the disclosure of the coding sequence of a human MDM2 mRNA at SEQ ID NO: 2 and also understood that Applicants had possession of sequences complementary to the human MDM2 mRNA sequences because of the well known rules of complementary base pairing. Applicant has argued that, furthermore, one skilled in the art would have understood that Applicants were in possession of oligonucleotides comprising a nucleotide sequence complementary to the human mRNA sequences and which would inhibit transcription or translation of a human MDM2 gene (pgs. 4-5).

However, this argument is not persuasive because, contrary to Applicant's arguments, one of skill in the art at the time the instant invention was made, could not envision, from knowledge of the primary nucleotide sequence of an mRNA, the particular structure of an antisense oligonucleotide that could be any antisense sequence that was complementary (including sequences that were fully complementary) to any portion of any human MDM2 mRNA (including at least pre-mRNAs, mature mRNAs and transcript variants), that would function commensurate with what is now claimed, that would inhibit the transcription or translation of any human

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MDM2 mRNA *in vitro*, in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein. This is made clear by the state of the art as shown by James 1991 (Antiviral Chemistry and Chemotherapy, Vol. 2(4), 191-214 who states, "Most studies that are published concern one antisense RNA that is inhibitory (frequently covering the entire mRNA; Table 1) and one is aware of a much larger number that do not appear in print which show that an antisense RNA does not inhibit. However, if one confines oneself to a consideration of experiments in which more than one antisense RNA is investigated it is clear that an investigation of the primary structure of an antisense RNA cannot predict whether or not it shall inhibit expression" and, "Since it seems that the primary sequence features of an antisense RNA do not determine whether it is inhibitor it is natural to look at other properties of the molecule such as length, secondary and tertiary structure ... [B]ut, once more, in experiments in which several AR genes have been examined there seems to be no simple relationship between length and degree of inhibition (pg. 198, col. 1).

The problems identified by James above were still recognized in the art of antisense even in 1998, wherein Branch states, in regards to the use of antisense oligonucleotides in cells (which that author characterizes as an *in vivo* application), "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a target number of candidates for their ability to act inside cells. Monia and co-workers used Northern hybridization to screen 34 20-nt long S-ODNs complementary to *c-ras*

kinase and found only one that yielded a greater than fivefold reduction in the target mRNA (Fig. 3a; Ref. 42). Thus, only 3% of the antisense molecules tested in this system were highly effective (Fig. 3b); 40% had almost no effect 42 (pg. 49, col. 1 bridge to col. 2).

Applicant has provided Exhibits A-L and asserted that these references demonstrate that antisense oligonucleotides complementary to a selected mRNA and that inhibited gene transcription or translation were readily made based on the sequence of the gene before the effective filing date of the Application, April 7, 1992. Applicant has concluded by arguing that, as shown by the Exhibits A-L, it was known in the art at the time of filing that antisense oligonucleotides capable of inhibiting transcription or translation of a gene could be successfully synthesized and used and that thus, the disclosure of the a coding sequence of a human MDM2 at SEQ ID NO: 2 would have conveyed that Applicants had possession of antisense oligonucleotides which are complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene in the claimed *in vitro* method of treating cells. However, contrary to Applicant's argument, Exhibits A-L are each drawn to genes other than an MDM2 gene. These references, when viewed in light of the James and Branch references provided above, demonstrate that the antisense disclosed to each target gene, respectively, was determined empirically but not that antisense oligonucleotides complementary to a selected mRNA and that inhibited gene transcription or translation were readily made based on the sequence of the gene.

The disclosure of the specification is extremely limited in regards to the methods of antisense inhibition as claimed and merely states, "A further object of the invention is to provide a method of treating a neoplastic human cell" (pg. 5) and "According to another embodiment of the invention, interference with the expression of MDM2 provides a therapeutic modality. The method can be applied *in vivo*, *in vitro*, or *ex vivo*. For example, expression may be down-regulated by administering triple-strand forming or antisense oligonucleotides which bind to the hMDM2 gene or mRNA, respectively, and prevent transcription or translation. The oligonucleotides may interact with unprocessed pre-mRNA or processed mRNA" (pg. 10, 3rd paragraph).

The specification discloses no examples of antisense oligonucleotides, thereby failing to set forth any representative species of antisense oligonucleotides from within the broad genus of antisense oligonucleotides as claimed. Moreover, neither the specification nor a search of the prior art at the time the invention was made, provides or points to a specific structure of an antisense oligonucleotide, as claimed, that would correspond with the function as claimed. The specification does not disclose any distinguishing identifying characteristics of the genera of antisense oligonucleotides complementary to any human MDM2 mRNA, that would function in the method as claimed, that would indicate that applicant was in possession of this broadly claimed genus. The specification, therefore, does not provide an adequate written description of the genus of methods of treating cells *in vitro* using antisense oligonucleotides as claimed, which would indicate that applicant was in possession of said genus. Additionally, the disclosure of the specification provides no specific guidance as to how

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one skilled in the art might be reasonably led to a particular species of the invention that would function commensurate with the scope what is now claimed, such that the invention would be complete and ready for patenting.

4. Claims 27, 28 and 56 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the Action mailed 2/28/2005 and below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention as set forth in claims 27, 28 and 56 is drawn to an *in vitro* method of treating a neoplastic cell or a cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein comprising administering a therapeutically effective amount of antisense oligonucleotides complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene. In the instant case, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use an *in vitro* method of treating a neoplastic cell or a cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein comprising administering antisense oligonucleotides which are complementary to human MDM2 mRNA, which inhibit transcription or translation of a human MDM2 gene.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 27, 28 and 56 are drawn to an *in vitro* method of treating a cell comprising administering antisense oligonucleotides that can be any antisense oligonucleotides that are complementary to any human MDM2 (including alleles and transcript variants) and that inhibit the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein.

The specification as filed, however, provides no support for claims to *in vitro* methods of treatment comprising administering antisense oligonucleotides of the invention that inhibit the transcription or translation of human MDM2 mRNA. The specification as filed provides no examples of treatment comprising administering antisense oligonucleotides of the invention and no guidance as to how to make or use the antisense oligonucleotides of the invention that will function to provide a treatment as claimed. The specification merely asserts that, "A further object of the invention is to provide a method of treating a neoplastic human cell" (pg. 5) and "According to another embodiment of the invention, interference with the expression of MDM2 provides a

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therapeutic modality. The method can be applied *in vivo*, *in vitro*, or *ex vivo*. For example, expression may be down-regulated by administering triple-strand forming or antisense oligonucleotides which bind to the hMDM2 gene or mRNA, respectively, and prevent transcription or translation. The oligonucleotides may interact with unprocessed pre-mRNA or processed mRNA" (pg. 10, 3rd paragraph). Moreover, the specification as filed provides no specific guidance that would allow the skilled artisan to recognize antisense oligonucleotides that will function in the methods of treatment as claimed.

The state of the art at the time the instant invention was made relative to the enablement of the antisense therapies *in vitro* recognized that there is a high degree of unpredictability in the art of applying antisense without direct evidence of a therapeutic effect due to numerous obstacles that continue, to the present day, to hinder the application of nucleic acid therapies, including for example, problems with delivery (including uptake by cells) and target accessibility (see above: James, Branch; below: Agrawal et al. and Rojanaskul).

At the time the instant invention set forth in claims 27, 28 and 56 was made and even 6 years later (the Branch reference), such obstacles were still relevant to the enablement of antisense inhibition of gene expression in cells (the instantly claimed methods are *in vitro*, in cells) (see below: Rojanaskul; Agrawal et al.). At the time the instant invention set forth in claims 27, 28 and 56 was made, the state of the art, as reviewed by Rojanaskul 1996 (Ad. Drug Deliv. Review. Vol. 18, pp. 115-131, summarized in Abstract), several years post filing, recognized that although oligonucleotide (ON) based therapy had advantages over traditional drugs, "their

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effective use has been limited due to several problems. For example, naturally occurring ONs contain phosphodiester backbones that are easily degraded in a biological environment and therefore must be protected or modified to render stability. In addition, because of their large molecular size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting, potential toxicity and affinity of ONs to the target sites pose major challenges to the successful utilization of these compounds” (Abstract, lines 8-13). Additionally, the post filing art of Agrawal et al. 2000 (Molecular Medicine Today, Vol. 61, pp. 72-81) indicates, in particular regard to antisense methods of treatment of cells *in vitro*, that, “*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors including cell type, kinetics of uptake, tissue culture conditions and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide. It is therefore appropriate to study each antisense oligonucleotide in its own context and relevant cell line without generalizing the results for every oligonucleotide” (pg. 80, col. 1, 1st paragraph).

The specification as filed provides no guidance that, at the time the invention was made, would have enabled the skilled artisan to have practiced the claimed antisense treatment methods over the broad scope claimed. The specification does not provide any examples of antisense treatments *in vitro*, in neoplastic cells or in cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein or provide any details related to the method of

treatment as claimed that would overcome the obstacles outlined above including the unpredictability of target site selection based on the knowledge of primary nucleotide sequence alone or even in combination with secondary and tertiary considerations, methods of delivery, the local concentration of antisense required to provide a treatment and the potential for non-antisense side effects, for example. Therefore, the specification does not provide, at the time the invention was made, the necessary and specific guidance by which one skilled in the art would have been enabled an *in vitro* method of antisense inhibition as claimed.

In order to practice the invention over the full scope claimed, at the time the invention was made, the skilled artisan would have needed to perform undue *de novo* trial and error experimentation, beyond the disclosure of the instant specification, in order to determine, at minimum, what particular antisense sequences that were complementary to a human MDM2 mRNA (which could be any human MDM2 mRNA) would function in a method *in vitro*, in a cell, and how to deliver the claimed antisense *in vitro*, at an effective concentration, to achieve a treatment. This undue *de novo* trial and error experimentation would have included the determination of such factors as accessible target sites that would have needed to be determined empirically and that were unpredictable from primary nucleotide sequence alone, dosage, route of administration, kinetics of uptake, disposition of the antisense molecule in cells and the half-life and stability of the antisense molecule *in vitro*. Given the art recognized unpredictability of the application of antisense *in vitro*, at the time the invention was made, this determination would not have been routine.

Therefore, based on the nature of the invention as a method of *in vitro* treatment in cells, the degree of unpredictability in the art of antisense oligonucleotide therapy *in vitro* at the time the invention was made, the breadth of the claimed methods as a method of treatment for any neoplastic cell or any cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein *in vitro*, the lack of specific guidance as to what particular species of antisense oligonucleotides would be required to practice the method as claimed, the need to screen multiple species of said oligonucleotides so as to allow identification of particular species as functional within the method of treatment as claimed and the quantity of *de novo* experimentation necessary to discover the above, an undue amount of experimentation would be required in order to practice the method of treatment as claimed. Therefore, the inventors have not enabled one skilled in the art to make and use the method of the claimed invention.

Response to Arguments

5. Applicant's arguments filed 5/31/2005 have been fully considered but they are not persuasive. Applicant has argued that to satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation, that the requirement for some experimentation is not fatal, but that the issue is whether the amount of experimentation required is undue and the test is not merely quantitative, because a

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considerable amount of experimentation is permissible if the experimentation is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (pg. 10, last paragraph bridge to the top of pg. 11).

However, this argument is not persuasive, because, as set forth in the prior Action and above, the amount of *de novo* trial and error experimentation that would be required to practice a method of inhibiting the expression of human MDM2 mRNA in a cell *in vitro*, in its full scope, based on the primary nucleotide sequence provided by Applicant as the coding region of a human MDM2 gene, would be undue in light of the art recognized unpredictability of a given antisense oligonucleotide to function to inhibit gene expression given primary nucleotide sequence alone.

Applicant argues that although the Agrawal, Rojanaskul, Opalinska, Jen, and Check references teach obstacles to using antisense oligonucleotides *in vitro*, these references teach, that despite these obstacles, antisense oligonucleotides complementary to a nucleotide sequence successfully inhibited a gene's transcription or translation *in vitro* and that thus, these references teach that antisense oligonucleotides complementary to a nucleotide sequence are able to inhibit a gene's transcription or translation despite any potential obstacles to the use of the antisense oligonucleotides *in vitro* (bottom of pg. 11, bridge to pg. 12).

However, this argument is not persuasive because the claims in the instant Application are drawn to methods of inhibiting the expression of a particular gene, the human MDM2 gene, *in vitro*, in a cell. The claims are not drawn generally to a

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composition comprising antisense oligonucleotides and the outstanding rejection is not directed to the composition of the antisense oligonucleotides themselves, but to the lack of enablement of a method of inhibiting human MDM2 gene expression in a cell *in vitro*.

Applicant also argues that one skilled in the art at the time the invention was made would have been able to make and use the recited antisense oligonucleotides which are complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene" in the claimed methods without resorting to undue experimentation because it was well known in the art, at the time the application was filed, how to make and use antisense oligonucleotides complementary to an mRNA sequence which inhibited transcription or translation of the mRNA's corresponding gene and that before the effective filing date of the application, April 7, 1992, the art taught how to make and use antisense oligonucleotides that inhibited transcription or translation of a target gene based on the target gene's sequence.

However, this argument is not persuasive because the claims in the instant Application are drawn to methods of inhibiting the expression of a particular gene, the human MDM2 gene, *in vitro*, in a cell. The claims are not drawn generally to a composition comprising antisense oligonucleotides and the outstanding rejection is not directed to the composition of the antisense oligonucleotides themselves, but to the lack of enablement of a method of inhibiting human MDM2 gene expression in a cell *in vitro*.

Applicant points to Exhibits A-L, filed with the instant response, and asserts that these exhibits demonstrate that at the time of the invention was made, the skilled artisan knew how to make and use antisense oligonucleotides that inhibited a gene's

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transcription or translation. It therefore would not have required undue experimentation for one of skill in the art to make and use antisense oligonucleotides which are complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene" for use in the claimed methods and that furthermore, any experimentation that would have been required to identify the recited antisense oligonucleotides would merely have been routine. As demonstrated in Exhibits A-L, the art routinely engaged in experimentation using antisense oligonucleotides that inhibited transcription or translation of a gene.

However, this argument is not persuasive because the claims in the instant Application are drawn to methods of inhibiting the expression of a particular gene, the human MDM2 gene, *in vitro*, in a cell. The claims are not drawn generally to a composition comprising antisense oligonucleotides and the outstanding rejection is not directed to the composition of the antisense oligonucleotides themselves, but to the lack of enablement of a method of inhibiting human MDM2 gene expression in a cell *in vitro*. Applicant's argument that any experimentation that would have been required to identify the recited antisense oligonucleotides would merely have been routine is not persuasive because the type of experimentation required to practice the invention more broadly than it is exemplified is a factor in the enablement analysis but it is not dispositive, in this case, the more or less standard nature of each type of experiment required to enable the invention is outweighed by the sheer quantity of experimentation required to practice the full scope of the claims, the unpredictability of the art generally and the

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claimed method in particular, and the lack of guidance in the specification regarding which direction the experimentation should proceed.

Claim Rejections - 35 USC § 102

6. The rejection of claims 58 and 60 under 35 U.S.C. 102(e) as being anticipated by Miraglia et al. (U.S. Patent 6,184,212) has been withdrawn in view of Applicants cancellation of claims 58 and 60, in the communication filed 5/31/05

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.


Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba



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